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09/518,190	03/02/00	HESKETH	J 0623.0820001

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EXAMINER

LANDSMAN, R
ART UNIT PAPER NUMBER

1647
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/518,190

Applicant(s)

HESKETH ET AL.

Examiner

Robert Landsman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 December 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.

- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

- A. Claims 1-8 were pending in the application. Claims 1-8 were canceled and new claims 9-22 have been added. Therefore, claims 9-22 are pending and are the subject of this Office Action.

2. Title

- A. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title should, for example, include the terms "nucleic acid molecules" and/or chimeras.

3. Claim Rejections - 35 USC § 112, first paragraph – lack of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

- A. Claims 9-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the constructs of Figure 1, does not reasonably provide enablement for all constructs comprising a deletion, insertion, or substitution in respect to all or part of a **3' untranslated region**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence

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of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is extensive with regard to claiming all nucleic acid constructs comprising a deletion, insertion, or substitution in respect to all or part of a 3' untranslated region. Applicants have stated in the specification, and the prior art teaches, that mRNA can and is transported to various locations in a cell (see, for example, Hesketh et al., especially the "Introduction" – references AS3 and AT3 on the Form PTO-1449). Applicants have provided minimal guidance and working examples as seen in Figure 1. However, Applicants do not provide enough guidance or working examples of nucleic acid constructs comprising a deletion, insertion, or substitution in respect to all or part of a 3' untranslated region. This is a critical aspect of this invention since Applicants desire nucleic acid molecules in which can be targeted to the ER, FP or CBPs, or wherein at least some of the encoded protein is synthesized in the ER. Since the 3'-untranslated region is critical in this targeting, it would be necessary to know the effect that a mutation in this region has on this targeting since Applicants desire a nucleic acid construct which is targeted to areas of the cell which allow the encoded protein to be secreted. It is not predictable to one of ordinary skill in the art what these critical nucleic acid residues in the 3'-untranslated region are which allow the targeting of these molecules to the desired locations in the cell.

In addition, the breadth of the claims 17-20 and 22 is extensive with regard to claiming all nucleic acid molecules which "**hybridize**" to the nucleic acid molecule of the invention. First, no stringency conditions are recited in the claim, meaning that even the lowest possible stringency conditions could be used in the hybridization assay. Nucleic acid molecules which "**hybridize**" to those nucleic acid molecules would have one or more nucleic acid substitutions, deletions, insertions and/or additions to the nucleic acid molecules of the invention. Furthermore, these nucleic acids would encode for proteins with one or more amino acid substitutions, deletions, insertions and/or additions to the protein encoded for by the nucleic acid of the invention.

Applicants provide no guidance or working examples of nucleic acid molecules which hybridize to the nucleic acid molecules of the invention, nor do they provide a *function* of these nucleic acid molecules, or of the proteins which they encode. Furthermore, it is not predictable to one of ordinary skill in the art what the functions of these nucleic acids, or the proteins which they encode, are.

In summary, the breadth of the claims is extensive with regard to Applicants claiming nucleic acid constructs comprising a deletion, insertion, or substitution in respect to all or part of a 3' untranslated region, or all nucleic acids which hybridize to those of the invention. There is also minimal guidance and working examples of these nucleic acid molecules and no guidance or working examples of nucleic acid molecules which hybridize to those of the invention. These factors, along with the lack of predictability to one of ordinary skill in the art as to what these critical nucleic acid residues in the 3'-untranslated region are which allow the targeting of these molecules to the desired locations in the cell, or of the function of these nucleic acid molecules which hybridize to those of the invention, or a function of the proteins which they encode, leads the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

4.Claim Rejections - 35 USC § 112, first paragraph – lack of written description

A. Claims and are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims since they read on all nucleic acid constructs comprising a deletion, insertion, or substitution in respect to all or part of a **3' untranslated region**. The specification provides a written description of only a small number of these nucleic acid constructs (Figure 1). No other species are described, or structurally contemplated, within the instant specification. The same reasons hold for claims 17-20 and 22 regarding nucleic acid molecules which “**hybridize**” to those of the invention. The scope of the claims includes numerous structural variants, and the genus is highly variant because a

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significant number of structural differences between genus members is permitted. Although these types of changes are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the nucleic acids class are missing from the disclosure. No common structural attributes identify the members of the genus. Therefore, one skilled in the art cannot reasonably visualize or predict critical nucleic acid residues which would structurally characterize the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, "constructs comprising a deletion, insertion, or substitution in respect to all or part of a 3' untranslated region," or the nucleic acid molecule of claim 9 alone are insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

5.Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 9 is confusing since the claim does not recite that the nucleic acid molecule is isolated and purified. Therefore, the claims read on any cell which endogenously comprises these molecules. This rejection can be overcome if the claim is amended to recite "An isolated and purified nucleic acid molecule..." Claims 10-22 are rejected since they depend from rejected claim 9.

B. Claim 9 is also confusing since it sounds like the nucleic acid molecule is linked to a protein instead of the nucleic acid molecule encoding the protein. The claim should be amended to recite "...signal peptide, said peptide operatively linked..."

C. Regarding claim 12, the phrase "associated with" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

D. Claim 13 recites the limitation "growth hormone, milk protein, or albumin" in claim 9 regarding "protein[s] that would normally not be secreted from mammalian cells." There is insufficient antecedent basis for this limitation in the claim. Growth hormone, milk proteins and albumin are normally secreted from cells.

E. Regarding claim 17, the phrase "capable of hybridizing" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "or the like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d). This rejection can be overcome by amending the claim to recite "which hybridizes." Claims 18-20 and 22 are rejected since they depend from rejected base claims.

6. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

A. Claims 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Reference AT5 on the Form PTO-1449) in view of Hesketh et al. (Reference AS3 on the Form PTO-1449). The claims recite a nucleic acid molecule (DNA and mRNA) encoding a signal sequence and which has an altered 3'-UTR which direct the molecule to the ER, FP or CBP of a mammalian cell. The claims also recite nucleic acid molecules which hybridize to the nucleic acid molecules of the invention, vectors, host cells, and methods of obtaining proteins. Lee et al. teach the production of a fusion protein by use of an expression plasmid which also comprises a mammalian signal peptide. The signal sequence is linked to a sialyltransferase, a protein which is not normally secreted from cells. Lee et al. teach that the chimeric protein (sialyltransferase and signal peptide) encoded for by the DNA can be secreted from mammalian cells (page 552, right column; Figures 1 and 2). Lee et al. do not teach that the 3'-UTR of these nucleic acids can be altered by a deletion, insertion, or substitution of a nucleotide in this region in order to target the mRNA to various subcellular compartments, such as FPs and CBPs. However, Hesketh et al. do teach that *myc* and β -globin coding sequences can be targeted to various cellular compartments, including FPs and CBPs, by altering the 3'-UTR of the encoding mRNA or DNA (entire document, especially Figure 1 and Tables 1 and 2).

Therefore, it would have been obvious to one of ordinary skill in the art to have used the invention of Hesketh et al., who teach that DNA/mRNA coding sequences can be targeted to various cellular compartments, including FPs and CBPs, by altering the 3'-UTR of the encoding mRNA or DNA, in the invention of Lee et al., who teach a nucleic acid molecule of a protein which is not normally secreted by a cell (sialyltransferase) fused to a mammalian signal sequence, as well as vectors and host cells comprising these nucleic acids. The purpose of combining these two methods would have been to be able to produce secreted proteins which are not normally secreted by a cell in order to obtain larger quantities of the protein for purification and potential medical use. One of ordinary skill in the art would have been motivated to combine these methods since the ability to alter the 3'-UTR in order to further

increase the localization of the mRNA encoding the fusion proteins to subcellular compartments which are involved with producing secreted proteins would not only help to ensure that these mRNAs were successfully targeted to the appropriate organelle, but to increase the yield of secreted protein

B. Claim 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Reference AT5 on the Form PTO-1449) in view of Hesketh et al. and further in view of Maeda et al. (Reference AS6 on the Form PTO-1449). Claim 13 is written as if albumin is considered "a protein that would not normally be secreted from a mammalian cell." However, albumin is secreted from cells, as discussed in the above rejection of claim 13 under 35 USC 112, second paragraph. Therefore, in anticipation of a potential error in claim 13 regarding albumin, this rejection under 35 USC 103 is being made.

Claims 9 and 12 have been rejected over Lee et al. in view of Hesketh et al. as stated in the above rejection under 35 USC 103. Neither Lee et al. or Hesketh et al. teach the signal peptide is albumin. However, Maeda et al. do teach the use of albumin as a signal peptide (Abstract). It would have been obvious to one of ordinary skill in the art to have substituted the albumin signal sequence of Maeda et al. for the signal peptide of Lee et al. for the purposes of producing a fusion protein which can be secreted since it was well-known at the time of the invention that albumin is secreted from mammalian cells, therefore, to produce a fusion protein/chimera using any signal peptide in order to target the protein to be secreted to a desired location would have been obvious. This rejection will be withdrawn if Applicants demonstrate or argue that albumin is indeed a protein which is not normally secreted from a cell.

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Advisory information

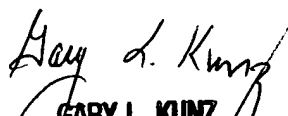
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
April 23, 2001


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